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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/009,945 | 06/21/2002 | Gerald H Thomsen | 10624-092 | 8725 |
| 20583 | 7590 | 05/03/2007 | EXAMINER | |
| JONES DAY | | | ROBINSON, HOPE A | |
| 222 EAST 41ST ST | | | ART UNIT | PAPER NUMBER |
| NEW YORK, NY 10017 | | | 1652 | |
| | | | MAIL DATE | DELIVERY MODE |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

| | | |
|------------------------------|------------------------|---------------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 10/009,945 | THOMSEN ET AL. |
| | Examiner | Art Unit |
| | Hope A. Robinson | 1652 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 10/17/06.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 69-72, 75, 78, 81-91, 102 and 103 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) 78, 87, 103 and 781 is/are allowed.
- 6) Claim(s) 69, 88-91 and 102 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 11 December 2001 is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____. |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____. | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| | 6) <input type="checkbox"/> Other: _____. |

DETAILED ACTION

Application Status

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1652.
2. Applicant's response to the Office Action mailed April 18, 2006 on October 17, 2006, is acknowledged.

Claim Disposition

3. Claims 69-72, 75, 78, 81-91 and 102-103 are pending and are under examination.

Maintained and Amended-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 69-72, 75, 88-91 and 102 remains rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to a method of screening for a modulator of Smurf activity. Claim 69 for example, has been amended to recite "the activity of Smurf comprising a WW domain and or a HECT domain and comprising greater than 90% identity with the amino acid sequence depicted in SEQ ID NO:2. Note that the recitation of the language "WW domain and or a HECT domain" provides some additional structural information, however, does not provide any functional limitation, as possession of a domain is not *per se* a function. In addition, claim 69 for example, 90% sequence similarity/identity, thus the claimed invention is directed to a large variable genus of proteins, however, the instant specification does not provide adequate description of the genus of polypeptides encompassed in the claims. There are no indicia as to conserved regions of for example SEQ ID NOS: 2 and 4 or where in the sequences the modifications will occur. The instant specification does not adequately describe variants of the claimed sequences by structure or any characteristics to indicate possession of the claimed variants. Further, the claims do not recite any functional limitation to indicate that once modified the protein will retain the specific Smurf activity (see for example claims 69, 75 and 90-91). It is noted that claims such as 70-71 and 88-89, recite a function (i.e. ubiquitination), however, the claims are directed to a large genus of polypeptides for which this function might not be retained and for which all the structural requirements are not met. Therefore, the skilled artisan cannot envision the detailed chemical structure of the polypeptides, thus, claims reciting % identity of the claimed sequences lacks adequate written description.

The specification fails to provide any additional representative species of the claimed genus to show that applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described, are representative of the entire genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

The claimed genus of polypeptides could include non-functional proteins or proteins with a different function than the one described. Therefore, the genus of claimed polypeptides encompasses widely variant species. As such, neither the description of the structure and function of SEQ ID NOS: 2 or 4, for example "90% identity to SEQ ID NO:2 ", is not sufficient to be representative of the attributes and features of the entire genus. Based on the unlimited variations contemplated one skilled in the art would at best expect a protein that is different or at worst a protein that is not functional.

Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or

she] invented what is claimed" (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. *See Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993).

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Response to Applicant's Arguments:

5. The amendment filed has been considered in full, however, it is not persuasive thus, the rejections of record remains. Applicant on page 6 of the response states that the claims have been amended to recite "90% identity in view of the revised written description guidelines that report 95%" pertaining to the written description rejection. The amendment made to the claims does not obviate the rejection of record because 90% sequence identity is not equivalent to the 95% stated in the revised guidelines. The claims still encompass a genus of variants not adequately described. Neither the claims or the specification provides any indication of where in the sequence variability can be tolerated to retain a functional protein, especially a protein that functions in the manner recited in the claims. The recited 90% is equivalent to minimally 72 residues that can be varied in the protein's structure anywhere in the 723 residue protein, including but not limited to deletions. The art recognizes that a single amino acid change can

have an adverse effect on the functionality of a protein and the claimed invention contemplates so much more. Thus, the rejection remains.

6. Claims 69-72, 75, 88-91 and 102 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the proteins set forth in SEQ ID NOS: 2/4 and the disclosure in Beach et al. (WO 97/12962, April 10, 1997), does not reasonably provide enablement for any polypeptide fragment of SEQ ID NOS: 2/4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The enablement requirement refers to the requirement that the specification describe how to make and how to use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: Quantity of Experimentation Necessary; Amount of direction or guidance presented; Presence or absence of working examples; Nature of the Invention; State of the prior art and Relative skill of those in the art; Predictability or unpredictability of the art and Breadth of the claims (see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). The factors most relevant to the instant invention are discussed below.

The amount of experimentation required to practice the claimed invention is undue as the claims encompass an unspecified amount of polypeptide fragments. The instant specification indicates that "Smurf proteins of the invention may contain at least about 5 and preferably at

least about 10 contiguous amino acids from the sequences set forth in SEQ ID NOS: 2/4" (see page 4). Page 21 of the specification provides a definition of what is considered to be "substantially homologous/similar" and page 24 of the instant specification discloses that derivatives or analogs are encompassed that are functionally active, i.e. capable of exhibiting one or more functional activities associated with a full-length wild type Smurf. However, the instant specification does not demonstrate any fragments of the claimed sequence having a Smurf activity. It is noted that the prior art discloses ubiquitin ligases (E3) with a sequence that is 77% and 99% identical to the claimed sequences (SEQ ID NO:2 and 4, respectively), however, the disclosed reference does not enable a sequence that is 90%, 91%, 92% to for example SEQ ID NO:2. Additionally, there is no demonstration of such a sequence having the desired activity. The instant protein could be non-functional or have a different function, thus, a skilled artisan would not know what activity to monitor in the claimed method absent guidance/direction. A large quantity of experimentation would be necessary to generate the infinite number of fragments recited in the claims and possibly screen same for activity and with the lack of guidance/direction provided in the instant specification, this is merely an invitation to the skilled artisan to use the current invention as a starting point for further experimentation. Thus, undue experimentation would be required for a skilled artisan to make and/or use the claimed invention commensurate in scope with the claims.

Predictability of which potential changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (for example, expectedly intolerant to modification), and detailed knowledge of the

ways in which the protein's structure relates to its function. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, for example, multiple substitutions. In this case, the necessary guidance has not been provided in the specification. Therefore, while it is known in the art that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. It is also known in the art that a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases. For example, various sites or regions directly involved in binding activity and in providing the correct three-dimensional spatial orientation of binding and active sites can be affected (see Wells, Biochemistry, vol. 29, pages 8509-8517, 1990). The instant specification provides no guidance/direction as to which regions of the protein would be tolerant of modifications and which would not, and it provides no working examples of any variant sequence that is encompassed by the claims. It is in no way predictable that randomly selected mutations, such as deletions, substitutions, additions, etc., in the disclosed sequences would result in a protein having activity comparable to the one disclosed. As plural substitutions for example are introduced, their interactions with each other and their effects on the structure and function of the protein is unpredictable. The skilled artisan would recognize the high degree of unpredictability that all the fragments encompassed in the claims would retain the recited function.

The state of the prior art provides evidence for the high degree of unpredictability as stated above. Seffernick et al. (J. Bacteriology, vol. 183, pages 2405-2410, 2001) disclose two

polypeptides having 98% sequence identity and 99% sequence identity, differing at only 9 out of 475 amino acids (page 2407, right column, middle and page 2408, Fig. 3). The polypeptides of Seffernick et al. are identical along relatively long stretches of their respective sequences (page 2408, Fig. 3), however, these polypeptides exhibit distinct functions. The modifications exemplified in the Seffernick et al. reference is small compared to those contemplated and encompassed by the claimed invention.

The specification lacks adequate guidance/direction to enable a skilled artisan to practice the claimed invention commensurate in scope with the claims. Furthermore, while recombinant and mutagenesis techniques are known in the art, it is not routine in the art to screen large numbers of mutated proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in certain activity, which is very complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's function from mere sequence data are limited, therefore, the general knowledge and skill in the art is not sufficient, thus the specification needs to provide an enabling disclosure.

The working examples provided do not rectify the missing information in the instant specification pertaining to the claimed variant. The nature and properties of this claim is difficult to ascertain from the examples provided as one of skill in the art would have to engage in undue experimentation to construct the variants of the claimed invention and examine the same for function.

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The specification does not provide support for the broad scope of the claims, which encompass an unspecified amount of fragments. The claims broadly read on any fragment thereof for the given sequences (SEQ ID NO: 2/4). The issue in this case is the breadth of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record. This make and test position is inconsistent with the decisions of *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

Thus, for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention as the amount of experimentation required is undue, due to the broad scope of the claims, the lack of guidance and working examples provided in the specification and the high degree of unpredictability as evidenced by the state of the prior art, attempting to construct and test variants of the claimed invention would constitute undue experimentation. Making and testing the infinite number of possible variants to find one that functions as described is undue experimentation. Therefore, applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner that reasonably correlates with the scope of the claims, to be considered enabling.

Response to Arguments

7. The applicant on pages 9+, state that the claimed invention is enabled and that the claims as amended to not encompass the variability the examiner specifies. This argument is not persuasive. As stated above pertaining to the written description rejection, the instant claims contemplate modifications to at least 72 residues throughout the structure of the protein, including substitutions, deletions etc. If for example 70 residues are deleted from the protein structure in one area or throughout the protein's structure, this could have an adverse effect on the protein's function in terms of inactivity or a different activity. The art reports that a change of a cysteine to an alanine in a HECT domain led to a change in activity, and said organism experiencing this modification would still comprise a HECT domain as recited in the claim (JMB, vol 282, pages 933-946, Saleh et al., 1998). Thus, applicant's arguments are not persuasive. Therefore, for all these reasons and the reasons of record the rejection remains.

Conclusion

8. No claims are allowable.

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9. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hope Robinson, MS
Primary Examiner
[Handwritten signature]
4/30/07

HOPE ROBINSON
PRIMARY EXAMINER